PA ∶NT COOPERATION TREAT

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

Commissioner
US Department of Commerce
United States Patent and Trademark
Office, PCT
2011 South Clark Place Room
CP2/5C24
Arlington, VA 22202
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 04 May 2001 (04.05.01)	
International application No. PCT/GB00/03460	**Applicant's or agent's file reference** REP06372WO
International filing date (day/month/year) 08 September 2000 (08.09.00)	**Priority date** (day/month/year) 08 September 1999 (08.09.99)
Applicant FENG, You-Min et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

16 March 2001 (16.03.01)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland** Facsimile No.: (41-22) 740.14.35	Authorized officer Olivia TEFY Telephone No.: (41-22) 338.83.38

PATENT COOPERATION TREATY

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INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference REP06372WO	**FOR FURTHER ACTION**	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
International application No. PCT/GB 00/ 03460	International filing date *(day/month/year)* 08/09/2000	(Earliest) Priority Date *(day/month/year)* 08/09/1999
Applicant SHANGHAI INSTITUTE OF BIOTECHNOLOGY		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 3 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

   a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   [ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

   b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

   [X] contained in the international application in written form.

   [X] filed together with the international application in computer readable form.

   [ ] furnished subsequently to this Authority in written form.

   [ ] furnished subsequently to this Authority in computer readble form.

   [ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   [ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [ ] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (see Box II).

4. With regard to the **title,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. ______

   [ ] as suggested by the applicant.

   [ ] because the applicant failed to suggest a figure.

   [ ] because this figure better characterizes the invention.

   [X] None of the figures.

INTERNATIONAL SEARCH REPORT

International Application No
PC[illegible] 00/03460

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07K14/62 A61P3/10

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

CHEM ABS Data, EPO-Internal, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	KRISTENSEN, CLAUS ET AL: "Alanine scanning mutagenesis of insulin" J. BIOL. CHEM. (1997), 272(20), QQ12978-12983, 16 May 1997 (1997-05-16), XP002141113 page 12981, left-hand column, paragraph 2 -page 12983, left-hand column, paragraph 1; table I	2,4,5

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
19 December 2000	04/01/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Fuhr, C

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	CHEMICAL ABSTRACTS, vol. 125, no. 21, 18 November 1996 (1996-11-18) Columbus, Ohio, US; abstract no. 266145, WANG, QIONG-QING ET AL: "Studies on receptor binding site of insulin: the hydrophobic B12Val can be substituted by hydrophilic Thr" XP002141114 cited in the application abstract & BIOCHEM. MOL. BIOL. INT. (1996), 39(6), 1245-1254, 1996,	1,3
A	EP 0 046 979 A (HOECHST AG) 10 March 1982 (1982-03-10) page 3, line 13 - line 25	1
A	EP 0 291 863 A (HOECHST AG) 23 November 1988 (1988-11-23) column 5, line 32 - line 51	1
A	US 5 618 913 A (BRANGE JENS J V ET AL) 8 April 1997 (1997-04-08) column 2, line 46 -column 4, line 16	1-14
X	BRANGE, J. ET AL: "Monomeric insulins obtained by protein engineering and their medical implications" NATURE (LONDON) (1988), 333(6174), 679-82, 16 June 1988 (1988-06-16), XP000026600 see compound B12Val-> Glu + des-B30 table 1	1
X	DATABASE CHEMABS 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; JENSEN, IVAN ET AL: "Scintigraphic studies in rats: kinetics of insulin analogs covering wide range of receptor affinities" retrieved from STN Database accession no. 115:224155 CA XP002155230 abstract & DIABETES (1991), 40(5), 628-32 , 1991,	1

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INTERNATIONAL SEARCH REPORT

Inform[redacted]on patent family members

International Application No
PC[redacted] 00/03460

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0046979 A	10-03-1982	DE 3033127 A	08-04-1982
		AT 4591 T	15-09-1983
		AU 545399 B	11-07-1985
		AU 7488381 A	11-03-1982
		CA 1173388 A	28-08-1984
		DE 3160852 D	13-10-1983
		DK 388081 A,B,	04-03-1982
		ES 505039 D	16-08-1982
		ES 8206448 A	16-11-1982
		JP 57077655 A	15-05-1982
		ZA 8106085 A	25-08-1982
EP 0291863 A	23-11-1988	DE 3717370 A	01-12-1988
		AT 71842 T	15-02-1992
		AU 601280 B	06-09-1990
		AU 1648788 A	24-11-1988
		CA 1335924 A	13-06-1995
		DE 3867903 A	05-03-1992
		DK 278088 A	23-11-1988
		ES 2032896 T	01-03-1993
		FI 882354 A,B,	23-11-1988
		GR 3004344 T	31-03-1993
		HU 46546 A,B	28-11-1988
		IE 60649 B	10-08-1994
		IL 86452 A	21-02-1993
		JP 63303930 A	12-12-1988
		NO 175641 B	01-08-1994
		NZ 224715 A	26-04-1990
		PH 25587 A	08-08-1991
		PT 87523 A,B	31-05-1989
		US 5028587 A	02-07-1991
		ZA 8803599 A	25-01-1989
US 5618913 A	08-04-1997	AT 113061 T	15-11-1994
		AU 593274 B	08-02-1990
		AU 6206686 A	05-03-1987
		CA 1306212 A	11-08-1992
		CN 86106574 A,B	03-08-1988
		CS 8606310 A	12-09-1990
		DE 3650101 D	24-11-1994
		DE 3650101 T	23-02-1995
		DK 411686 A,B,	03-03-1987
		EP 0214826 A	18-03-1987
		ES 2001624 A	01-06-1988
		FI 863512 A	01-03-1987
		GR 862233 A	31-12-1986
		HU 42526 A	28-07-1987
		HU 206518 B	30-11-1992
		IE 66138 B	13-12-1995
		IL 79887 A	21-11-1991
		JP 2662390 B	08-10-1997
		JP 62053999 A	09-03-1987
		KR 9400756 B	29-01-1994
		LU 90484 A	21-02-2000
		NO 177009 B	27-03-1995
		NZ 217406 A	29-05-1989
		PH 25772 A	18-10-1991
		YU 4188 A	30-06-1990

Form PCT/ISA/210 (patent family annex) (July 1992)

INTERNATIONAL SEARCH REPORT

Informa[redacted]n patent family members

International Application No
PC[redacted] 00/03460

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5618913 A		YU 148486 A	30-04-1991
		ZA 8606450 A	27-05-1987
		PT 83278 A,B	01-09-1986

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PATENT COOPERATION TREATY

REC'D 09 JAN 2002

WIPO PCT

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference REP06372WO	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/GB00/03460	International filing date *(day/month/year)* 08/09/2000	Priority date *(day/month/year)* 08/09/1999
International Patent Classification (IPC) or national classification and IPC C07K14/62		
Applicant SHANGHAI INSTITUTE OF BIOCHEMISTRY, et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 1 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand 16/03/2001	Date of completion of this report 04.01.2002
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Roscoe, R Telephone No. +49 89 2399 2554

Form PCT/IPEA/409 (cover sheet) (January 1994)

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

   Description, pages:

   1-7 as originally filed

   Claims, No.:

   1-5 as received on 20/11/2001 with letter of 19/11/2001

   Drawings, sheets:

   1/1 as originally filed

   Sequence listing part of the description, pages:

   1-2, as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☒ contained in the international application in written form.

   ☒ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority in written form.

   ☐ furnished subsequently to this Authority in computer readable form.

   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	
	No:	Claims	1-5
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-5
Industrial applicability (IA)	Yes:	Claims	1-5
	No:	Claims	

2. Citations and explanations
   see separate sheet

V. Reasoned statement on Novelty, Inventive St p and Industrial Applicability

The documents mentioned in the present International Preliminary Examination Report are numbered as in the search report, i.e. D1 corresponds to the first document of the search report etc.

- **Novelty (Art.33(2) PCT)**

D1 discloses B12Ala and B16Ala mutants which were converted to des-B30 derivatives. Further, B26Ala is provided. As a result, D1 anticipates claims 15. Claims to a product cannot generally be rendered novel by a use i.e. "for therapeutic use". This feature has to be read as "suitable for therapeutic use" in the present situation. There is no reason to believe that the products in D1 were not suitable for therapeutic use.

D2 discloses substitution of B12Val by Leucine or threonine. B12Leu had substantially reduced receptor binding activity and general activity. B12Thr nearly had w.t. values. D2 is presumably reason why mere B12 mutant not claimed in claim 2. Does not anticipate present claims but obviously intrinsically provides monomeric insulin.

D3 discloses insulin wherein Thr 30 can be optionally removed and Phe 1 is removed from the B chain. Des-B1 insulin had a substantially improved solubility and reduced immunogenicity. Des-B30 mutation further reduced immunogenicity which is a major problem during prolonged administration. Both single and double mutants provide fast-acting and stable insulin. B30 is only difference between human and pig insulin. Rmoval renders sequences of both same and thus can use pig as source of cheaper des-B30 insulin. Does not suggest modifications at positions 12, 16, 26 so not anticipatory.

D4 discloses use of des-B1 and des-B30 mutants which can be combined with addition of Arg at positions B31 and B32. Regulates speed of action. Little relevance.

D5 discloses preparation of fast-acting insulin analogs with reduced tendency to

self-associate into multimeric forms. Preferably replace amino acids with other more hydrophilic amino acids. Asp, Glu, Ser, Thr, His or Ile are preferred substitutes. The formula of the claimed compounds is given in col.3. All compounds may have one or more amino acids removed from N or C terminal end of B-chain (top col.4). Residues at positions 12, 16 and 26 may be modified. Col.6 defines specific combinations of substitutions which include B12, 16 and 26 substitutions (also B12 + B16, B12 + B26). These substitutions can clearly be combined with B1 or B30 deletions. However, in order to select present insulins need to effectively take features from two lists (terminal options / internal options), hence novelty acknowledged over general disclosure.

D6 discloses the design of monomeric insulins. Particularly suggests modifying residues B12 and B26 (see p.679, top col.2). Table 1 shows a B12Val>Glu desB-30 derivative. Further shows B26Tyr>Glu.

D7 discloses B12V>E substitution.

- **Inventive Step (Art.33(3) PCT)**

Since none of the present claims are novel, inventive step need not be considered. Nevertheless, the following is noted:

Since combinations of internal modifications with terminal modifications are taught in the prior art, as are modifications at positions 12, 16 and 26 (see e.g. D5), inventive step can only be acknowledged if applicant can prove that his selections are purposive and result in surprising properties.

D5 is the closest prior art - as D6 it addresses the problem of providing monomeric insulins and involves changes at positions B16 and B26, yet the emphasis is on introducing hydrophilic amino acids, not Alanine. Had applicant provided any formally novel claims, it seems that inventive step could have been acknowledged on this basis and in view of experimental data.

- **Industrial Applicability (Art.33(4) PCT)**

The present claims appear to have industrial applicability.